REMARKS

Claims 74-133 were pending in the present application. Claims 94 and 103-133 have been canceled without prejudice to or disclaimer of the subject matter contained therein. Claim 74 was amended to include subject matter from claim 94. Claims 96-98 were amended to reflect the cancellation of claim 94. Claims 89-91 were amended to further clarify the meaning thereof. No new matter was added. Claims 74-93 and 95-102 are now pending.

Applicants appreciate the helpful interview with the Examiner on June 19, 2006, wherein the cited art and rejected claims were discussed.

Reexamination of the application and reconsideration of the rejections are respectfully requested in view of the above amendments and the following remarks, which follow the order set forth in the Office Action.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 89-91 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

According to the Office Action, the claims indicate that the composition contains at least one additive but then indicates that the amount of the additive can be 0% which renders the claim ambiguous. Applicants have amended these claims to further clarify the meaning thereof by including the phrase "up to". This meaning is the same as previously indicated but has been presented in order to expedite prosecution by clarifying that some amount of additive according to the claim will be present. Claims including a maximum amount such as a claim of "less than" a particular amount have been found allowable. *See, In re Kirsch, 498 F.2d 1389, 1394, 182 USPQ 286 (CCPA 1974).*

In the *Kirsch* case, in a claim directed to a chemical reaction process, a limitation required that the amount of one ingredient in the reaction mixture should "be maintained at less than 7 mole percent" based on the amount of another ingredient. The examiner argued that the claim was indefinite because the limitation sets only a maximum amount and is inclusive of substantially no ingredient resulting in termination of any reaction. The court did not agree because the claim was clearly directed to a reaction process which did not warrant distorting the overall meaning of the claim to preclude performing the claimed process. *498 F.2d at 1394.* The same reasoning is applicable here. *Also see, MPEP § 2173.05(c)II.* Claims 89-91 require that the composition further comprises at least one additive from a

particular group present in an amount up to the amount given; thus, some amount of at least one additive must be present in the composition. This meaning of the claims is clear and definite since to interpret the claim otherwise would distort the meaning of the claim which requires the composition to include some amount of at least one of the additives listed. In view thereof, claims 89-91 are definite and Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Rejection 1

Claims 74-133 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Clark et al., U.S. Patent No. 5,981,621, in view of Kronenthal et al., U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203 and EP 965623. Applicants respectfully traverse this rejection.

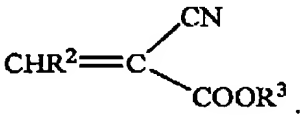
Claim 74 is directed to a biocompatible adhesive composition comprising a first monomer species comprising an alkyl ester cyanoacrylate, a second monomer species different from the first monomer species comprising an alkyl α-cyanoacrylate, and a polymerization initiator or accelerator comprising a quaternary amine. The first and second monomer species have different polymer absorption rates and the biocompatible adhesive composition has a third polymer absorption rate different than the polymer absorption rates of the monomer species.

The mixture of at least two different monomer species where the different monomer species have different polymer absorption rates allows for adjustment and tailoring of the degradation rate of the resultant formed polymer. *Specification, page 4, lines 5-13.* The selection of monomer will affect the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. Two or more different monomers that have varied absorption and/or polymerization rates may be used in combination to give a greater degree of control over the absorption rate of the resultant polymer, as well as the polymerization rate of the monomer. The selection of the monomer and initiator as taught in the specification provide control within relatively narrow and predictable ranges for both the polymerization and absorption rates. *Specification, page 10, lines 7-14.*

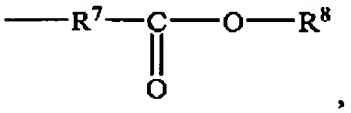
The disclosure of each cited patent is described separately below. A discussion of the rejection of the claims over the combination of the cited art follows thereafter.

Clark et al., U.S. Patent No. 5,981,621

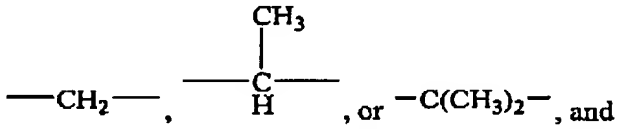
Clark et al. discloses a wound closure monomer composition comprising (A) at least one monomer, which forms a medically acceptable wound closure polymer, (B) at least one plasticizing agent, and (C) at least one acidic stabilizing agent. *Column 2, line 64-column 3, line 2.* Clark et al. discloses that preferred monomers have the formula



As disclosed, R^2 is hydrogen and R^3 may be, among other things, a group having the formula



wherein R^7 is



R^8 is an organic radical. *Column 4, lines 7-35.* Claim 10 of Clark et al. recites a composition of claim 1 wherein the composition comprises at least two different monomers. Clark et al. also discloses that initiators that initiate polymerization and/or cross-linking of the material may be applied to a surface portion or to the entire surface of the applicator tip, including the interior and the exterior of the tip, and that the suitable initiators include cationic surfactants such as benzalkonium chloride. *Column 11, lines 18-67.*

Claim 74 is now the only pending independent claim. The elements of claim 74 include the following:

(a) a biocompatible adhesive composition comprising:

(b) a first monomer species comprising (b1) an alkyl ester cyanoacrylate,

(c) a second monomer species different from the first monomer species comprising (c1) an alkyl α-cyanoacrylate, and

(d) a polymerization initiator or accelerator comprising a quaternary amine,

(e) wherein the first monomer species has a first polymer absorption rate

(f) and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate

(g) and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

Clark et al. lacks disclosure of at least a combination of (b1) and (c1) and disclosure of any of (e), (f) or (g). Rather, while Clark et al. claims the use of two different monomers, the types of monomers which should be used is not disclosed. Moreover, Clark et al. does not describe the biodegradability or absorption rate of any polymerized compositions.

Kronenthal et al., U.S. Patent No. 3,995,641

Kronenthal et al. discloses carbalkoxyalkyl 2-cyanoacrylates. *Abstract.* Monomeric carbalkoxyalkyl 2-cyanoacrylates may be employed individually or as comonomers in biological adhesive compositions. *Column 2, lines 5-7.* As stated in the Description of the Prior Art, an object of the Kronenthal et al. invention "is to provide cyanoacrylate monomers which can be used either alone or as comonomers in the bonding of similar or dissimilar materials without the use of heat or catalyst during the bonding operation. Comonomer compositions are of interest for specific uses because they may provide advantageous combinations of properties not completely embodied in individual monomers." *Column 1, lines 44-51.*

Kronenthal et al. describes alkyl 2-cyanoacrylates as having failed to have the required properties of low toxicity and adequate absorption by the tissues. The Kronenthal et al. specification states that methyl 2-cyanoacrylate gives rise to a severe inflammatory response at the site of application and the n-butyl and isobutyl 2-cyanoacrylate monomers are not absorbed well (if at all) by the tissues. *Column 1, lines 14-33.*

As described above, claim 74 has the following elements:

(a) a biocompatible adhesive composition comprising:

(b) a first monomer species comprising (b1) an alkyl ester cyanoacrylate,

(c) a second monomer species different from the first monomer species comprising (c1) an alkyl α-cyanoacrylate, and

(d) a polymerization initiator or accelerator comprising a quaternary amine,

(e) wherein the first monomer species has a first polymer absorption rate

(f) and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate

(g) and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

Kronenthal et al. lacks disclosure of at least elements (c) and (c1) and disclosure of any of (d), (e), (f) or (g). The only combination of monomers described in Kronenthal et al. is a combination of monomeric carbalkoxyalkyl 2-cyanoacrylates, not any combination of different monomers. A description of any combination of monomers with different absorption rates is completely lacking. Moreover, as pointed out in the present specification, Kronenthal et al. does not disclose the use of initiators, but rather indicates that blood and other body fluids polymerize the monomers. The disclosure of Kronenthal et al. also does not address the effect of the selection of initiators on the properties possessed by cyanoacrylates or polymerization products thereof. *Specification, page 2, lines 23-27.*

Hammerslag, U.S. Patent No. 6,386,203

Hammerslag discloses methods and compositions for closing and sealing a wound, laceration, incision, or other percutaneous opening using an adhesive. Preferred sealing media comprise cyanoacrylates combined with fumed silica. *Abstract.*

As described above, claim 74 has the following elements:

(a) a biocompatible adhesive composition comprising:

(b) a first monomer species comprising (b1) an alkyl ester cyanoacrylate,

(c) a second monomer species different from the first monomer species comprising (c1) an alkyl α-cyanoacrylate, and

(d) a polymerization initiator or accelerator comprising a quaternary amine,

(e) wherein the first monomer species has a first polymer absorption rate

(f) and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate

(g) and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

Hammerslag lacks disclosure of at least elements (c), (d), (e), (f) and (g). According to Hammerslag, formulations of sealing media preferably comprise a tissue adhesive such as a cyanoacrylate which has been modified to increase its viscosity and, preferably decrease its polymerization rate. *Column 5, lines 7-10.* Hammerslag additionally states:

> Examples of adhesive compounds include cyanoacrylates and fibrin based adhesives. Polymerizable cyanoacrylates that have been cross-linked or co-polymerized ***with other compounds*** that may alter elasticity, modify viscosity, aid biodegradation or change some other property of the resulting material may also be used as adhesive compounds in accordance with the present invention. For example, polyacrylic acid having a molecular weight of

200,000 to 600,000 may be cross-linked to a cyanoacrylate to form compounds which may allow the absorbability to be coordinated with the tissue regeneration rate and may feature higher elasticity than cyanoacrylates alone. Absorbability is unnecessary for topical applications, in which the adhesive film will simply fall off in a few days.

Column 5, lines 22-34 (emphasis added).

Hammerslag further describes biodegradation of polymers made from monomers:

> There is a wide variation in the rates and facility of in vivo biodegradation of polymers made from monomers which may be used as adhesive compounds in the present invention. There is also a wide variation in such rates among the members of the cyanoacrylate family, the preferred adhesive compounds of the present invention. Generally, polymers of cyanoacrylates which have substituents that are small and/or contain one or more oxygen-containing functional groups (e.g. ether, ester, carbonyl) appear to have increased biodegradability rates. Cyanoacrylates having long chain alkyl groups lacking in oxygen-containing functional groups as substituents may tend to form polymers which biodegrade more slowly. There are also indications in the literature that the biodegradation rate of cyanoacrylate polymers is affected by the polymer molecular weight and crystallinity of the polymer.
>
> There are several studies of biodegradation rates of polymers formed by various members of the cyanoacrylate family in the scientific and medical literature. It is within the abilities of one of skill in the art to use such information in the literature along with routine experimentation in order to ***choose a member of the cyanoacrylate family*** with suitable biodegradation characteristics for use in accordance with the present invention.

Column 6, lines 32-48 (emphasis added). None of the extensive description in Hammerslag regarding bioabsorbability relates to use of monomer species with differing absorption rates or combinations of different types of cyanoacrylate monomers. The only reference to using cyanoacrylate monomers gives the example of cross-linking with polyacrylic acid. There is no suggestion to use a combination of different cyanoacrylate monomers.

EP 965 623 to Malofsky et al.

EP 0965623 discloses an adhesive composition including a polymerizable adhesive monomer, at least one vapor phase stabilizer, and at least one liquid phase stabilizer. *Abstract.* The monomer may be a cyanoacrylate. Claim 5 recites that the monomer is at least one member selected from the group consisting of n-butyl cyanoacrylate, 2-octyl cyanoacrylate, ethyl cyanoacrylate, methyl cyanoacrylate, ethoxyethyl cyanoacrylate, and methoxyethyl cyanoacrylate. No other combinations of monomers are described.

As described above, claim 74 has the following elements:

(a) a biocompatible adhesive composition comprising:

(b) a first monomer species comprising (b1) an alkyl ester cyanoacrylate,

(c) a second monomer species different from the first monomer species comprising (c1) an alkyl α-cyanoacrylate, and

(d) a polymerization initiator or accelerator comprising a quaternary amine,

(e) wherein the first monomer species has a first polymer absorption rate

(f) and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate

(g) and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

EP '623 lacks disclosure of at least elements (b1) and (e), (f) and (g). The EP '623 publication mentions providing an absorbable or non-absorbable material for biomedical applications, but does not describe the use of monomer species with different polymer absorption rates. Moreover, EP '623 does not describe any combinations of monomers except those in claim 5 which are alkyl cyanoacrylates or other cyanoacrylates; alkyl ester cyanoacrylates are not included.

The Obviousness Rejection

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must some suggestion or motivation, either in the references themselves or in the knowledge in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the cited art reference or references when combined must teach or suggest all the claim limitations. *See MPEP § 2143.*

According to the Office Action, the difference between the prior art and the claimed invention is that the prior art does not expressly disclose a composition or film having a first monomer, which includes alkyl ester cyanoacrylate, and a different second monomer where the absorption rate of the first monomer species is different from the absorption rate of the second monomer species. *Office Action mailed March 27, 2006, page 4.* Applicants agree that there is at least this difference between the cited art and subject matter defined in the rejected claims.

The Office Action then concludes as follows:

> However, the prior art amply suggests the same as the prior art discloses the combination of different monomers in forming medical adhesives. Further, ***it would have been well within the skill*** of and one of ordinary skill in the art would have been motivated to combine an alkyl ester cyanoacrylate with a different cyanoacrylate, such as an octyl 2-cyanoacrylate or alkylether cyanoacrylate, with the expectation that biodegradation of the composition could be adjusted readily by modifying the ratio of the monomers and the composition would have a low degree of inflammatory response.

Office Action mailed March 27, 2006, page 4 (emphasis added). Applicants disagree.

First, the cited art refers to a combination of different monomers but none of the cited art describes or suggests the use of a combination of an alkyl ester cyanoacrylate and an alkyl α-cyanoacrylate as claimed. Clark et al. does not indicate which different monomers should be used. Kronenthal et al. only discloses combining different alkyl ester cyanoacrylate monomers. Hammerslag only discloses or suggests the use of a cyanoacrylate monomer with a different type of monomer, suggested to be a non-cyanoacrylate monomer. EP '623 specifically recites only certain alkyl cyanoacrylates or alkyl ether cyanoacrylates in combination; alkyl esters in combination with alkyl α-cyanoacrylates are not disclosed or suggested.

Moreover, no suggestion to modify the teachings of the cited art has been provided. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). No suggestion of the combination as claimed is found in the cited art or a combination thereof. In addition, no suggestion to modify the disclosures of the cited art to provide the combination of monomers as claimed is found in the art.

Clark et al. does not describe any use of monomers for purposes of absorbability, and does not describe or suggest the particular combination of monomers defined in the rejected claims.

Kronenthal et al. is only directed to ester cyanoacrylates which are absorbable in mammalian tissue and notes that alkyl cyanoacrylates are <u>not</u> absorbed well. *Column 1, lines 14-33.* A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Thus, Kronenthal et al. would have led one of ordinary skill in the art <u>away</u> from any combination of monomers including an alkyl cyanoacrylate.

Hammerslag does not describe or suggest the use of any combination of cyanoacrylate monomers. Rather, Hammerslag suggests the use of polymerizable cyanoacrylates that have been cross-linked or co-polymerized with **other compounds**. Hammerslag states that there is a wide variation in rates and facility of in vivo biodegradation of members of the cyanoacrylate family and describes the differences including indicating that it is within the abilities of one of skill in the art to use information in the literature along with routine experimentation to choose **a member** of the cyanoacrylate family with suitable biodegradation characteristics. Nothing in the disclosure of Hammerslag suggests combining different cyanoacrylate monomers as claimed.

EP '623 includes a claim which could provide combinations of certain specific cyanoacrylate monomers. None of these monomers is an ester cyanoacrylate. Moreover, EP '623 does not disclose or suggest that any combination of monomers would provide advantages in absorbability.

Thus, even in combination, the cited art would not have led one of ordinary skill in the art to composition as defined in the rejected claims. The only specific teaching regarding absorbability is in Kronenthal et al., which would have led one away from the use of an α-alkyl cyanoacrylate.

Second, the Office Action states that is would have been well within the skill of one of ordinary skill in the art to make the combination as claimed. However, such a statement is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine and/or modify the teachings of the cited art. *See, MPEP § 2143.01 IV; Ex parte Levengood*, 28 USPQ2d 1300 (BPAI 1993). Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the monomers claimed in combination with an initiator or accelerator comprising a quaternary amine for the invention as defined in the rejected claims. *In re Kotzab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000) (No finding as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of Kotzab's invention to make the combination in the manner claimed.). No such reason has been provided. To the contrary, Applicants have provided evidence that the selection of monomer and initiator as taught in the specification would not have been obvious to one of ordinary skill in the art. The cited art does not discuss or even acknowledge the problem of selecting cyanoacrylate monomer species with different absorption rates and initiators for use therefore such that polymerization of the combination will provide an

adhesive composition with an absorption rate different from either of the monomers. As detailed in the attached pages from Odian, "Principles of Polymerization" 3rd edition (1991), John Wiley and Sons, Inc., pp. 496-503, the reactivity of comonomer systems with different initiators may be difficult to predict. The selection of particular cyanoacrylate monomer species with an initiator or accelerator comprising a quaternary amine as defined in the rejected claims to obtain a polymer or adhesive composition is not disclosed or suggested by any combination of the cited art. *See, specification, page 13, lines 26-31 and Declaration Under 35 U.S.C. § 1.132, paragraph 3 (submitted December 20, 2005).*

Thus, not only is there is no motivation or suggestion to combine and modify the cited art as required for a *prima facie* case of obviousness, but the second requirement for obviousness is also not met since there is no reasonable expectation of success found in the cited art. As shown by the Principles of Polymerization book, the effect of initiators with comonomers may be unpredictable. None of the cited art provides any disclosure, suggestion or guidance as to how to combine the monomers as claimed to provide a biocompatible adhesive composition. Thus, the monomer selection and an appropriate initiator or accelerator must be present as claimed to provide the desired adhesive composition. Given the unpredictability in this area, and the teachings of Kronenthal et al. away from the use of an α-alkyl cyanoacrylate, there would not have been any expectation of success in providing an adhesive composition with the advantageous properties found from the combination of the cited art.

The final requirement for a *prima facie* case of obviousness is that all the claim limitations must be taught or suggested by the prior art. The Office Action states:

> Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Office Action mailed March 27, 2006, page 5. From the foregoing, it is clear that not every element of the invention has been taught. Rather, each and every cited document lacks any teaching or suggestion regarding at least features (e), (f) and (g) of claim 74:

(e) wherein the first monomer species has a first polymer absorption rate

(f) and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate

(g) and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

In addition, none of the cited art discloses or suggests the combination of a monomer species comprising an alkyl ester cyanoacrylate and a monomer species comprising an alkyl α-cyanoacrylate with an initiator or accelerator comprising a quaternary amine.

If the invention as defined in the rejected claims is considered as a whole, and the cited art documents are considered in their entirety, it is clear that the cited art, alone or in combination, does not disclose or suggest the biocompatible adhesive composition as claimed. In view thereof, Applicants respectfully request that this rejection be withdrawn.

Rejection 2

Claims 74-133 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Clark et al., U.S. Patent No. 5,981,621, in view of Kronenthal et al, U.S. Patent No. 3,995,641, Hammerslag, U.S. Patent No. 6,386,203 and EP 965623, in further view of Banitt et al., U.S. Patent No. 3,559,652, and Collins et al. Applicants respectfully traverse this rejection.

Clark et al., Kronenthal et al., Hammerslag and EP '623 are discussed in detail above. Banitt et al., is directed to a method for surgically adhering living tissues and effecting hemostasis therein by means of a rapidly polymerizing composition which comprises alkoxyalkyl 2-cyanoacrylates. *Abstract.*

As discussed, claim 74 has the following elements:

(a) a biocompatible adhesive composition comprising:

(b) a first monomer species comprising (b1) an alkyl ester cyanoacrylate,

(c) a second monomer species different from the first monomer species comprising (c1) an alkyl α-cyanoacrylate, and

(d) a polymerization initiator or accelerator comprising a quaternary amine,

(e) wherein the first monomer species has a first polymer absorption rate

(f) and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate

(g) and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

Banitt et al. lacks at least features (b1), (c), (f) and (g). The alkoxyalkyl 2-cyanoacrylates of Banitt et al. are described as providing the desired absorbability, in contrast to alkyl cyanoacrylates. Banitt et al. does disclose a combination of alkoxyalkyl 2-cyanoacrylates and alkyl cyanoacrylates (*column 4, lines 1-7*) but does not mention or

suggest the use of an alkyl ester cyanoacrylate, alone, or in combination with any other monomer. Additionally, Banitt et al. does not describe or suggest the use of monomers with differing absorption rates with a polymerization initiator or accelerator comprising a quaternary amine to provide a polymer absorption rate as desired.

Collins et al. describes cure rates of cyanoacrylate tissue adhesives. In particular, Collins et al. compares rates of polymerization for the series of *N*-alkyl-2-cyanoacrylates, methyl through octyl. Collins et al. does not describe combinations of cyanoacrylate monomers and only describes tests on alkyl 2-cyanoacrylates, not other types of cyanoacrylate monomers. At best, Collins et al. notes that an adhesive having properties of the methyl monomer and properties of the higher homologues would be desirable. No disclosure or suggestion of how to obtain such an adhesive is provided. To the contrary, the disclosure of Collins et al. details the different rates of polymerization of cyanoacrylates and points out that the polymerization rates in water are different from those in blood. Thus, Collins et al. supports the position of Applicants that one of ordinary skill in the art would not have known that the cyanoacrylate monomers as claimed could be combined to provide a single polymer, given the differing polymerization rates, and the unknown factors implicit in Collins et al. wherein the polymerization rates are different in different situations.

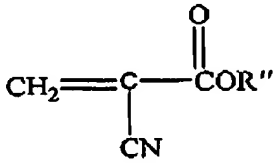
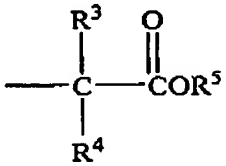
Banitt et al. and Collins et al. do not add any subject matter or motivation to combine or modify the cited art which would have led one of ordinary skill in the art to the invention as defined in the rejected claims. As noted, none of the art discloses or suggests a combination of a monomer species comprising alkyl ester cyanoacrylate with a monomer species comprising alkyl α-cyanoacrylate with a polymerization initiator or accelerator comprising a quaternary amine. Moreover, none of the art, alone or in combination, describes or suggests an adhesive wherein the first monomer species has a first polymer absorption rate, and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate, and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

In view of the foregoing, a *prima facie* case has not been made, and Applicants respectfully request that this rejection be withdrawn.

Rejection 3

Claims 74-102 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Berger et al., U.S. Patent No. 5,998,472, in view of Kronenthal et al., Hammerslag and Clark et al. Applicants respectfully traverse this rejection.

Berger et al. discloses that the addition of a C_{10}-C_{12} alkyl cyanoacrylate ester to a C_1 to C_8 alkyl cyanoacrylate ester provides for a composition which forms a flexible cyanoacrylate polymer on mammalian skin without the need to add a plasticizer. *Column 2, lines 62-67.* Berger et al. also discloses the following:

> ... it is contemplated that the flexibility of polymeric films formed on mammalian skin from cyanoacrylate esters can be improved by the addition of a effective amount of a C_{10} to C_{12} cyanoacrylate ester wherein such cyanoacrylate esters are represented by the formula
>
> 
>
> wherein R" is alkenyl of 2 to 10 carbon atoms, cycloalkyl groups of from 5 to 8 carbon atoms, phenyl, 2-ethoxyethyl, 3-methoxybutyl, or a substituent of the formula:
>
> 
>
> wherein R^3 and R^4 are independently selected from the group consisting of hydrogen and methyl, and R^5 is selected from the group consisting of alkyl of from 1 to 6 carbon atoms, alkenyl of from 2 to 6 carbon atoms, alkynyl of from 2 to 6 carbon atoms, cycloalkyl of from 3 to 8 carbon atoms, aralkyl selected from the group consisting of benzyl, methylbenzyl and phenylethyl, phenyl, and phenyl substituted with 1 to 3 substituents selected from the group consisting of hydroxy, chloro, bromo, nitro, alkyl of 1 to 4 carbon atoms, and alkoxy of from 1 to 4 carbon atoms.

Column 10, line 53-column 11, line 18.

As discussed, claim 74 has the following elements:

(a) a biocompatible adhesive composition comprising:

(b) a first monomer species comprising (b1) an alkyl ester cyanoacrylate,

(c) a second monomer species different from the first monomer species comprising (c1) an alkyl α-cyanoacrylate, and

(d) a polymerization initiator or accelerator comprising a quaternary amine,

(e) wherein the first monomer species has a first polymer absorption rate

(f) and the second monomer species has a second polymer absorption rate different from the first polymer absorption rate

(g) and the biocompatible adhesive composition has a third polymer absorption rate different from the first and second polymer absorption rates.

Berger et al. lacks at least features (d), (e), (f) and (g) of claim 74. In addition, Berger et al. does not disclose any information regarding absorbability since the adhesive disclosed in Berger et al. is intended for use "on" skin. As discussed above, each of Kronenthal et al., Hammerslag and Clark et al. lack at least features (e), (f) and (g) of claim 74. The combination of the cited art would not have made the invention as defined in the rejected claims obvious since the combination of particular monomers with a polymerization initiator or accelerator comprising a quaternary amine to obtain a particular absorption rate is not suggested thereby. Rather, the combination of Berger et al. and Kronenthal et al. would have led one of ordinary skill in the art concerned about absorbability away from the use of alkyl α-cyanoacrylates given the disclosure in Kronenthal et al. regarding the poor absorbability of those types of cyanoacrylate monomers. Indeed, Hammerslag also would have led one of skill in the art to a different conclusion than the combination claimed, given the specific disclosure therein to use cyanoacrylate monomers with other compounds that may alter elasticity, modify viscosity, aid biodegradability or change some other property. In view thereof, the combination of art cited would not have made the invention as defined in the rejected claims obvious, but, rather, would have led one of ordinary skill in the art to a different type of adhesive with different monomers than those claimed. Thus, a *prima facie* case has not been made and Applicants respectfully request that this rejection be withdrawn.

For the foregoing reasons, claims 74-93 and 95-102 are considered allowable. A Notice to this effect is respectfully requested. If any questions remain, the Examiner is invited to contact the undersigned at the number given below.

Respectfully submitted,

HUTCHISON LAW GROUP PLLC

Date: July 20, 2006

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Attachment: Odian, "Principles of Polymerization"
3rd edition (1991), John Wiley and Sons, Inc.,
pp. 496-503

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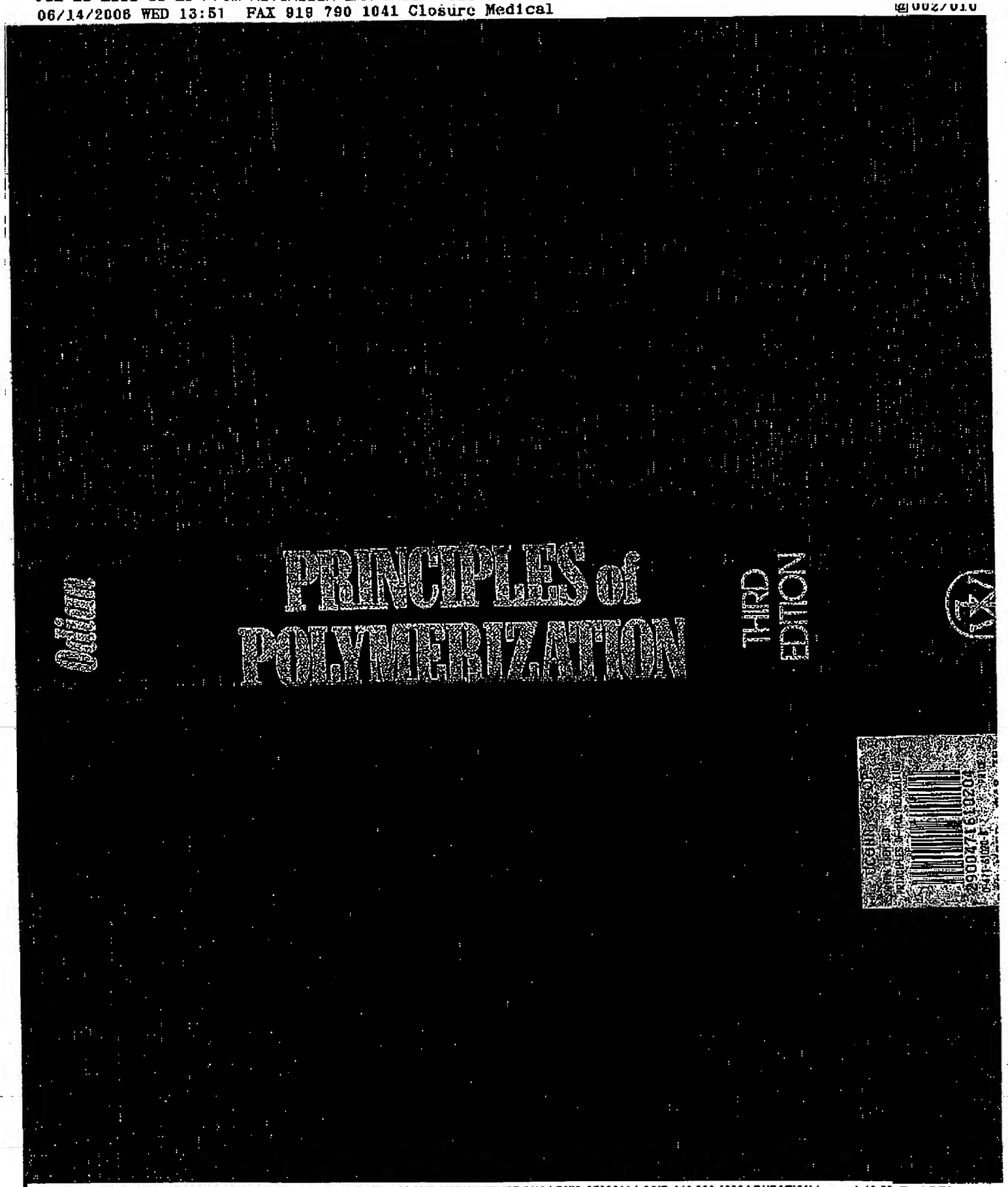

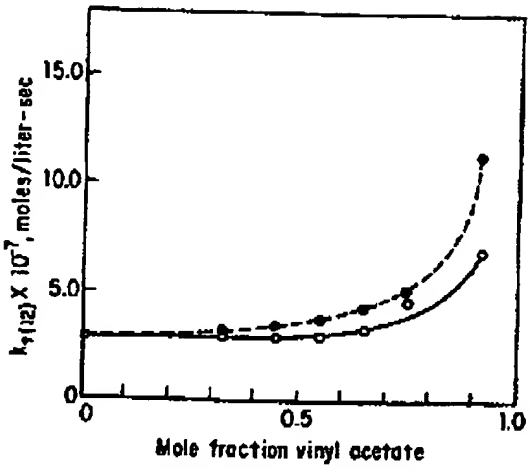

Fig. 6-14 Dependence of the termination rate constant $k_{t(12)}$ on the mole fraction of vinyl acetate in the radical copolymerization of vinyl acetate–methyl methacrylate. The solid-line plot and open circles represent calculations by Eq. 6-73; the broken-line plot and solid circles represent calculations by Eq. 6-72. After Atherton and North [1962] (by permission of the Faraday Society, London).

The utility of Eq. 6-72 in correlating copolymerization data has been established in several studies [O'Driscoll et al., 1967; Prochazka and Kratochvil, 1983]. Thus, Fig. 6-14 shows the experimentally determined $k_{t(12)}$ values (i.e., the values calculated from Eq. 6-72) for vinyl acetate–methyl methacrylate copolymerization (dotted curve). The expected variation of $k_{t(12)}$ with the comonomer (and copolymer) composition can be handled by Eq. 6-72, whereas Eq. 6-67 with a single ϕ value is not applicable. Figure 6-14 also shows the $k_{t(12)}$ values calculated via Eq. 6-73 from the copolymer composition and the termination rate constants for the two homopolymerizations (solid curve). Equation 6-73 appears to be qualitatively but not quantitatively valid. Evidently, the method of weighting the k_{t11} and k_{t22} values directly with the copolymer composition is not correct. Refinements of this treatment have included expressing $k_{t(12)}$ as a function of the viscosity of the reaction medium and introducing penultimate considerations into the termination process [Braun and Czerwinski, 1989].

6-4 IONIC COPOLYMERIZATION

Ionic copolymerizations are different from radical copolymerizations in several respects. Ionic copolymerizations are much more selective. The number of comonomer pairs that undergo either cationic or anionic copolymerization is relatively limited because of the wider range of monomer reactivities in ionic copolymerization [Bywater, 1976; Kennedy and Marechal, 1983; Morton, 1983]. Cationic copolymerization is limited to monomers with electron-donating substituents and anionic copolymerization to monomers with electron-withdrawing substituents. For comonomer pairs that undergo ionic copolymerization, the general tendency is toward the ideal type of behavior (Sec. 6-2c-1), with the r_1r_2 product approaching unity, where the relative reactivities of the two monomers toward the two different ionic propagating centers are approximately

the same. There is a general lack of any tendency toward alternation. Furthermore, quite a few copolymerizations proceed with r_1r_2 values greater than unity. Thus there are relatively few monomer pairs that yield copolymers containing large proportions of both monomers.

Another characteristic feature of ionic copolymerizations is the sensitivity of the monomer reactivity ratios to changes in the initiator, reaction medium, or temperature. This is quite different from the behavior observed in radical copolymerization. Monomer reactivity ratios in radical copolymerization are far less dependent on reaction conditions.

6-4a Cationic Copolymerization

6-4a-1 *Reactivity*

The effect of a substituent on the reactivity of a monomer in cationic copolymerization depends on the extent to which it increases the electron density on the double bond and on its ability to resonance stabilize the carbocation that is formed. However, the order of monomer reactivities in cationic copolymerization (as in anionic copolymerization) is not nearly as well defined as in radical copolymerization. Reactivity is often influenced to a larger degree by the reaction conditions (solvent, counterion, temperature) than by the structure of the monomer. There are relatively few reports in the literature in which monomer reactivity has been studied for a wide range of different monomers under conditions of the same solvent, counterion, and reaction temperature.

Among the most extensive studies of monomer reactivity have been those involving the copolymerization of various meta- and para-substituted styrenes with other styrene monomers (styrene, α-methylstyrene, and p-chlorostyrene) as the reference monomer [Kennedy and Marechal, 1983]. The relative reactivities of the various substituted styrenes have been correlated by the Hammett sigma–rho relationship

$$\log\left(\frac{1}{r_1}\right) = \rho\sigma \tag{6-74}$$

For example, $\log(1/r_1)$ values for a series of meta- and para-substituted styrenes copolymerized with styrene were plotted against the sigma substituent constants to yield a straight line with slope ρ of negative sign. The sigma value of a substituent is a quantitative measure of that substituent's total electron-donating or electron-withdrawing effect by both resonance and induction. Electron-withdrawing and electron-donating substituents have positive and negative sigma constants, respectively. A negative value of ρ means $1/r_1$ is increased by electron-donating substituents as expected for cationic polymerization. (A positive value of ρ would mean $1/r_1$ is increased by electron-withdrawing substituents.) Substituents increase the reactivity of styrene in the approximate order

$$\underset{(-0.27)}{p\text{-}OCH_3} > \underset{(-0.17)}{p\text{-}CH_3} > \underset{(0)}{p\text{-}H} > \underset{(+0.23)}{p\text{-}Cl} > \underset{(+0.37)}{m\text{-}Cl} > \underset{(+0.71)}{m\text{-}NO_2}$$

which follows the order of their electron-donating effect as indicated by the sigma values shown in parentheses. More recently $\log(1/r_1)$ for meta- and para-substituted styrenes has been correlated with the ^{13}C NMR chemical shifts of the β-carbon of the

substituted styrenes [Hatada et al., 1977; Wood et al., 1989]. Similar correlations have been observed for the cationic copolymerizations of para-substituted benzyl vinyl ethers with benzyl vinyl ether. The correlation of log ($1/r_1$) with chemical shift (δ) is analogous to the correlation with σ, since both δ and σ measure the electron-donating ability of the substituent.

Although the Hammett-type approach is most useful for the quantitative correlation of monomer reactivity with structure, it is applicable only to substituted styrenes. One is, however, usually more interested in the relative reactivities of the commonly encountered monomers such as isoprene, acrylonitrile, and isobutene. The appropriate quantitative data are relatively sparse for these monomers. The generally observed order of monomer reactivity is

vinyl ethers > isobutylene > styrene, isoprene

which is the order expected on the basis of the electron-pushing ability of the various substituents. Monomers with electron-pulling substituents such as acrylonitrile, methyl methacrylate, and vinyl chloride show negligible reactivity in cationic copolymerization. There has been some success in correlating log ($1/r_1$) with the e values from the Q–e scheme [Ham, 1977].

Steric effects similar to those in radical copolymerization are also operative in cationic copolymerizations. Table 6-9 shows the effect of methyl substituents in the α- and β-positions of styrene. Reactivity is increased by the α-methyl substituent due to its electron-pushing power. The decreased reactivity of β-methylstyrene relative to styrene indicates that the steric effect of the β-substituent outweighs its polar effect of increasing the electron density on the double bond. Furthermore, the trans-β-methylstyrene appears to be more reactive than the cis isomer, although the difference is much less than in radical copolymerization (Sec. 6-3b-2). It is worth noting that 1,2-disubstituted alkenes have finite r values in cationic copolymerization compared to the values of zero in radical copolymerization (Table 6-2). There is a tendency for 1,2-disubstituted alkenes to self-propagate in cationic copolymerization, although this tendency is nil in the radical reaction.

6-4a-2 *Effect of Solvent and Counterion*

It has previously been shown that large changes can occur in the rate of a cationic polymerization by using a different solvent and/or different counterion (Sec. 5-2f). The monomer reactivity ratios are also affected by changes in the solvent or counterion. The effects are often complex and difficult to predict since changes in solvent or counterion often result in alterations in the relative amounts of the different types of

TABLE 6-9 Steric Effects in Copolymerization of α- and β-Methylstyrenes (M_1) with *p*-Chlorostyrene (M_2)[a,b]

M_1	r_1	r_2
Styrene	2.31	0.21
α-Methylstyrene	9.44	0.11
trans-β-Methylstyrene	0.32	0.74
cis-β-Methylstyrene	0.32	1.0

[a]Data from Overberger et al. [1951, 1954, 1958].
[b]$SnCl_4$ in CCl_4 at 0°C.

propagating centers (free ion, ion pair, covalent), each of which may be differently affected by solvent. As many systems do not show an effect as do show an effect of solvent or counterion on r values [Kennedy and Marechal, 1983]. The dramatic effect that solvents can have on monomer reactivity ratios is illustrated by the data in Table 6-10 for isobutylene-*p*-chlorostyrene. The aluminum bromide-initiated copolymerization shows $r_1 = 1.01$, $r_2 = 1.02$ in *n*-hexane but $r_1 = 14.7$, $r_2 = 0.15$ in nitrobenzene. The variation in r values has been attributed to the preferential solvation of propagating centers in the nonpolar medium (*n*-hexane) by the more polar monomer (*p*-chlorostyrene). The increased concentration of *p*-chlorostyrene at the reaction site results in its greater incorporation into the copolymer than expected based on the composition of the comonomer feed in the bulk solution. Calculation of r values using the bulk comonomer feed composition results in a lower value of r_1 coupled with a higher value of r_2. In the polar nitrobenzene the propagating centers are completely solvated by the solvent without participation by *p*-chlorostyrene, and the more reactive isobutylene exhibits its greater reactivity.

The effect of solvent on monomer reactivity ratios cannot be considered independent of the counterion employed. Again, the situation is difficult to predict with some comonomer systems showing altered r values for different initiators and others showing no effects. Thus the isobutylene–*p*-chlorostyrene system (Table 6-10) shows different r_1 and r_2 for $AlBr_3$ and $SnCl_4$. The interdependence of the effects of solvent and counterion are shown in Table 6-11 for the copolymerization of styrene and *p*-methylstyrene. The initiators are listed in order of their strength as measured by their effectiveness in homopolymerization studies. Antimony pentachloride is the strongest initiator and iodine the weakest. The order is that based on the relative concentrations of different types of propagating centers. Polymerizations by iodine and trichloroacetic proceed predominantly through covalent species while ion pairs and free ions are involved for polymerizations with the other initiators.

The data in Table 6-11 show the copolymer composition to be insensitive to the initiator for solvents of high polarity (1,2-dichloroethane and nitrobenzene) and also insensitive to solvent polarity for any initiator except the strongest ($SbCl_5$). The styrene content of the copolymer decreases with increasing solvent polarity when $SbCl_5$ is the initiator. The styrene content also decreases with decreasing initiator strength for the low-polarity solvent (toluene). These results can be interpreted in terms of the effect of solvent and counterion on the identity of the propagating centers and on the extent of preferential solvation of propagating centers by one of the monomers. In the styrene–*p*-methylstyrene system *p*-methylstyrene is both the more polar and the more reactive of the two monomers. In the poor solvent (toluene) the monomers compete, against the solvent, with each other to solvate the propagating centers (primarily ion pairs for all initiators other than iodine and trichloroacetic acid). The more polar *p*-

TABLE 6-10 Effect of Solvent and Initiator on r Values

r_1 Isobutylene	r_2 *p*-Chlorostyrene	Solvent	Initiator
1.01	1.02	*n*-C_6H_{14} (ε 1.8)	$AlBr_3$
14.7	0.15	ϕ-NO_2 (ε 36)	$AlBr_3$
8.6	1.2	ϕ-NO_2 (ε 36)	$SnCl_4$

[a]Data from Overberger and Kamath [1959].
[b]Temperature: 0°C.

TABLE 6-11 Effects of Solvent and Counterion on Copolymer Composition in Styrene–*p*-Methylstyrene Copolymerization[a]

	% Styrene in Copolymer[b]		
Initiator System	Toluene (ϵ 2.4)	1,2-Dichloroethane (ϵ 9.7)	Nitrobenzene (ϵ 36)
$SbCl_5$	46	25	28
AlX_3	34	34	28
$TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, $SbCl_3$	28	27	27
Cl_3CCO_2H		27	30
I_2		17	

[a]Data from O'Driscoll et al. [1966].
[b]Comonomer feed = 1 : 1 styrene–*p*-methylstyrene.

methylstyrene preferentially solvates the propagating ion pairs and is preferentially incorporated into the copolymer. The selectivity increases in proceeding from $SbCl_5$ to $AlCl_3$ to the other initiators, which corresponds to increases in both the amount of ion pairs relative to free ions and amount of tight ion pairs relative to loose ion pairs. For the better solvents the counterion does not appreciably influence the reaction, since the monomers cannot compete with the solvent. In the $SbCl_5$ initiated copolymerization increasing the solvent power of the reaction medium also decreases the ability of the monomers to compete with the solvent to complex with propagating centers. The copolymer composition is then determined primarily by the chemical reactivities of the monomers.

6-4a-3 Effect of Temperature

Temperature has a greater influence on monomer reactivity ratios in cationic copolymerization than in radical copolymerization because of the greater spread of propagation activation energies for the ionic process. The ratio of any two rate constants is expected to tend toward unity with increasing temperature since the smaller rate constant (larger activation energy) will increase faster with increasing temperature than the larger rate constant (smaller activation energy). However, there is no general trend of r values tending toward unity (i.e., less selective reaction) in cationic copolymerization with increasing temperature as there is radical copolymerization. Some r values increase with temperature and others decrease. Various combinations of effects have been observed for different comonomer pairs [Kennedy and Marechal, 1983]. There are comonomer systems where both r_1 and r_2 tend toward unity as expected, but there are also many systems where an r value decreases below or increases above unity with increasing temperature. This unexpected behavior is probably the result of changes in the identities and relative amounts of different propagating species (free ion, ion pair, covalent) either directly as a result of a change in temperature, or indirectly by the effect of temperature on solvent polarity.

6-4b Anionic Copolymerization

6-4b-1 Reactivity

Monomer reactivities in anionic copolymerization are the opposite of those in cationic copolymerization. Reactivity is enhanced by electron-withdrawing substituents that

decrease the electron density on the double bond and resonance stabilize the carbanion formed. Although the available data is rather limited [Bywater, 1976; Morton, 1983; Szwarc, 1968], reactivity is generally increased by substituents in the order

$$—CN > —CO_2R > —\phi, —CH=CH_2 > —H$$

The reactivity of monomers with electron-releasing substituents in anionic copolymerization is nil. Correlation of reactivity in copolymerization with structure has been achieved in some studies [Favier et al., 1977; Shima et al., 1962].

The general characteristics of anionic copolymerization are very similar to those of cationic copolymerization. There is a tendency toward ideal behavior in most anionic copolymerizations. Steric effects give rise to an alternating tendency for certain comonomer pairs. Thus the styrene–*p*-methylstyrene pair shows ideal behavior with $r_1 = 5.3$, $r_2 = 0.18$, $r_1r_2 = 0.95$, while the styrene–α-methylstyrene pair shows a tendency toward alternation with $r_1 = 35$, $r_2 = 0.003$, $r_1r_2 = 0.11$ [Bhattacharyya et al., 1963; Shima et al., 1962]. The steric effect of the additional substituent in the α-position hinders the addition of α-methylstyrene to α-methylstyrene anion. The tendency toward alternation is essentially complete in the copolymerizations of the sterically hindered monomers 1,1-diphenylethylene and *trans*-1,2-diphenylethylene with 1,3-butadiene, isoprene, and 2,3-dimethyl-1,3-butadiene [Yuki et al., 1964].

6-4b-2 *Effects of Solvent and Counterion*

Monomer reactivity ratios and copolymer compositions in many anionic copolymerizations are altered by changes in the solvent or counterion. Table 6-12 shows data for styrene–isoprene copolymerization at 25°C by *n*-butyl lithium [Kelley and Tobolsky, 1959]. As in the case of cationic copolymerization, the effects of solvent and counterion cannot be considered independently of each other. For the tightly bound lithium counterion, there are large effects due to the solvent. In poor solvents the copolymer is rich in the less reactive (based on relative rates of homopolymerization) isoprene because isoprene is preferentially complexed by lithium ion. (The complexing of 1,3-dienes with lithium ion is discussed further in Sec. 8-6b). In good solvents preferential solvation by monomer is much less important and the inherent greater reactivity of styrene exerts itself. The quantitative effect of solvent on copolymer composition is less for the more loosely bound sodium counterion.

TABLE 6-12 Effect of Solvent and Counterion on Copolymer Composition in Styrene–Isoprene Copolymerization[a]

	% Styrene in Copolymer for Counterion	
Solvent	Na^+	Li^+
None	66	15
Benzene	66	15
Triethylamine	77	59
Ethyl ether	75	68
Tetrahydrofuran	80	80

[a]Data from Kelley and Tobolsky [1959].

Copolymerizations of nonpolar monomers with polar monomers such as methyl methacrylate and acrylonitrile are especially complicated. The effects of solvent and counterion may be unimportant compared to the side reactions characteristic of anionic polymerization of polar monomers (Sec. 5-3b-4). In addition, copolymerization is often hindered by the very low tendency of one of the cross-propagation reactions. For example, polystyryl anions easily add methyl methacrylate but there is little tendency for poly(methyl methacrylate) anions to add styrene. Many reports of styrene–methyl methacrylate (and similar comonomer pairs) copolymerizations are not copolymerizations in the sense discussed in this chapter. The initial product is essentially poly(methyl methacrylate) homopolymer. Little styrene is incorporated into copolymer chains until most or all of the methyl methacrylate is exhausted. Reports of significant amounts of styrene in products from anionic copolymerization of styrene–methyl methacrylate are usually artifacts of the particular reaction system, a consequence of heterogeneity of the propagating centers and/or counterion.

The anionic copolymerization of methyl methacrylate and styrene with lithium emulsion and *n*-butyllithium initiators is interesting [Overberger and Yamamoto, 1966; Richards, 1978; Tobolsky et al., 1958]. Bulk copolymerization of an equimolar mixture of the two monomers with a lithium emulsion yields a copolymer with a high percentage of styrene, whereas *n*-butyllithium yields a copolymer with essentially no styrene. Further, the product from the lithium emulsion reaction is essentially a block copolymer. The results with lithium emulsion have been attributed to insolubility of lithium counterion. The lithium ion is part of an insoluble lithium particle and propagation takes place on that particle surface. Styrene is more strongly adsorbed than methyl methacrylate on these surfaces because of its dense π-electron system. Reaction occurs with a very high styrene concentration at the reaction site and initial reaction involves a polystyryl homopropagation. At some point the propagating chains detach from the metal surface and become solubilized in the bulk solution where there is a much higher concentration of methyl methacrylate. Polystyryl anions quickly add methyl methacrylate with very little tendency for reverse crossover back to styrene, and the result is a block copolymer. On the other hand, polymerization initiated by *n*-butyllithium proceeds in solution from the very beginning. The greater reactivity of methyl methacrylate coupled with the very small tendency for crossover from poly(methyl methacrylate) propagating centers to polystyryl results in the product being essentially poly(methyl methacrylate) homopolymer. Copolymer with significant amounts of styrene is obtained only at higher conversion where the feed composition is low in methyl methacrylate.

6-4b-3 Temperature

There are few studies of the effect of temperature on monomer reactivity ratios [Morton, 1983]. For styrene–1,3-butadiene copolymerization by *s*-butyllithium in *n*-hexane, there is negligible change in r values with temperature with $r_1 = 0.03$, $r_2 = 13.3$ at 0°C and $r_1 = 0.04$, $r_2 = 11.8$ at 50°C. There is, however, a significant effect of temperature for copolymerization in tetrahydrofuran with $r_1 = 11.0$, $r_2 = 0.04$ at −78°C and $r_1 = 4.00$, $r_2 = 0.30$ at 25°C. The difference between copolymerization in polar and nonpolar solvents is attributed to preferential complexing of propagating

6-5 DEVIATIONS FROM TERMINAL COPOLYMERIZATION MODEL

The derivation of the terminal (or first-order Markov) copolymer composition equation (Eq. 6-12 or 6-15) rests on two important assumptions—one of a kinetic nature and the other of a thermodynamic nature. The first is that the reactivity of the propagating species is independent of the identity of the monomer unit, which precedes the terminal unit. The second is the irreversibility of the various propagation reactions. Deviations from the quantitative behavior predicted by the copolymer composition equation under certain reaction conditions have been ascribed to the failure of one or the other of these two assumptions or the presence of a comonomer complex which undergoes propagation.

6-5a Kinetic Penultimate Behavior

The behavior of some comonomer systems indicates that the reactivity of the propagating species is affected by the next-to-last or penultimate monomer unit. This behavior, referred to as *second-order Markov* or *penultimate* behavior, manifests itself in a particular copolymerization by giving inconsistent values of the monomer reactivity ratios for different comonomer feed compositions. This has been observed in many radical copolymerizations where the monomers contain highly bulky or polar substituents. Thus in the copolymerization of styrene (M_1) and fumaronitrile (M_2), chains rich in fumaronitrile and having styrene as the last added unit show greatly decreased reactivity with fumaronitrile monomer [Fordyce and Ham, 1951]. The effect is due to steric and polar repulsions between the penultimate fumaronitrile unit in the propagating chain and the incoming fumaronitrile monomer.

The mathematical treatment of the penultimate effect [Barb, 1953; Ham, 1964; Merz et al., 1946] in such a copolymerization involves the use of the eight propagating reactions

$$
\begin{aligned}
\sim\sim M_1M_1\cdot + M_1 &\xrightarrow{k_{111}} \sim\sim M_1M_1M_1\cdot \\
\sim\sim M_1M_1\cdot + M_2 &\xrightarrow{k_{112}} \sim\sim M_1M_1M_2\cdot \\
\sim\sim M_2M_2\cdot + M_1 &\xrightarrow{k_{221}} \sim\sim M_2M_2M_1\cdot \\
\sim\sim M_2M_2\cdot + M_2 &\xrightarrow{k_{222}} \sim\sim M_2M_2M_2\cdot \\
\sim\sim M_2M_1\cdot + M_1 &\xrightarrow{k_{211}} \sim\sim M_2M_1M_1\cdot \\
\sim\sim M_2M_1\cdot + M_2 &\xrightarrow{k_{212}} \sim\sim M_2M_1M_2\cdot \\
\sim\sim M_1M_2\cdot + M_1 &\xrightarrow{k_{121}} \sim\sim M_1M_2M_1\cdot \\
\sim\sim M_1M_2\cdot + M_2 &\xrightarrow{k_{122}} \sim\sim M_1M_2M_2\cdot
\end{aligned}
\tag{6-75}
$$

with the four reactivity ratios:

$$
\begin{aligned}
r_1 &= \frac{k_{111}}{k_{112}} \quad r_1' = \frac{k_{211}}{k_{212}} \\
r_2 &= \frac{k_{222}}{k_{221}} \quad r_2' = \frac{k_{122}}{k_{121}}
\end{aligned}
\tag{6-76}
$$